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Observations and Research

Management Decisions in Crohn's Disease Are Changed by Knowledge of Proactive and Reactive Testing of Antitumor Necrosis Factor Drug Levels

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Background: There is controversy about the proactive clinical application of therapeutic drug monitoring (TDM) of biologic drugs in Crohn's disease (CD). One way to practically assess this is to examine how TDM influences management decisions. We examined how knowledge of proactive and reactive antitumor necrosis factor (anti-TNF) drug levels changes management in a variety of clinical scenarios.

Methods: In this retrospective cohort study, all adults with CD having trough level infliximab or adalimumab measurements at Liverpool Hospital between June 2013 and July 2016 were included. Demographics, indications for testing, anti-TNF drug levels, and treatment details were collected along with subsequent management decisions. The decision made by the treating clinician after receiving the drug level was compared to a consensus decision from a panel of 3 gastroenterologists based on the clinical, laboratory, imaging, and/or endoscopic results without the drug level. When these 2 decisions were discrepant, the anti-TNF drug level was deemed to have changed management.

Results: One hundred and eighty-seven trough levels of infliximab or adalimumab from 108 patients were analyzed. Overall, assessment of anti-TNF levels affected management in 46.9% of the instances. Knowledge of the drug level was also more likely to result in management change when the test was performed for reactive TDM compared to proactive TDM (63% vs 36%, $P = .001$).

Conclusions: The addition of TDM of anti-TNF agents to routine investigations alters management decisions in adult CD patients on anti-TNF therapy in both proactive and reactive settings.

Lay Summary

A retrospective observational study that shows the addition of antitumor necrosis factor drug level to routine clinical parameters alters management decisions in adult Crohn's disease patients in both proactive and reactive settings.

Key Words: infliximab, adalimumab, therapeutic drug monitoring, Crohn's disease

Introduction

Antitumor necrosis factor-α (anti-TNF) therapy including infliximab (IFX) and adalimumab (ADA) has demonstrated efficacy in the induction and maintenance of steroid-free remission in patients with moderate to severe Crohn's disease (CD).[1–3] However, these agents are not impervious to treatment failure such as primary or secondary nonresponse with standard dosing.[4] The annual risk for loss of IFX response has been estimated to be 13% per patient-year.[5] Biologic therapeutic drug monitoring (TDM) refers to the measurement of biologic levels such as those of anti-TNF in order to individualize drug selection and dosing to improve patient outcomes.

In the reactive setting, TDM can be used to identify the underlying cause of secondary loss of response (LOR). Those with low trough drug levels and either undetectable or low antidrug antibodies have inadequate drug levels and can be successfully treated with an escalation of anti-TNF agents. Patients with secondary LOR and high circulating antidrug antibodies also do not respond to anti-TNF dose escalation, as antidrug antibodies bind to the circulating drug which leads to increased clearance and neutralization of drug effect.[6,7] Patients with pharmacodynamic failure have anti-TNF trough levels above a therapeutic threshold and an ongoing inflammatory process independent of the anti-TNF pathway. Hence, they are unlikely to respond to biological dose intensification

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and should be switched to another drug.[8–10] Yanai et al demonstrated that the presence of either therapeutic trough levels or high titer antidrug antibodies predicted failure to respond to dose escalation with 90% specificity.[11] Reactive TDM not only allows earlier implementation of effective treatment and avoids potentially unnecessary drug exposure, but it is also a cost-effective approach.[12,13] Another utilization of reactive TDM measurement is the investigation of adverse reactions. There is established evidence that persistently antidrug antibodies are associated with acute severe infusion reactions.[14]

In contrast to reactive TDM, the usefulness of proactive TDM, performed to mitigate secondary LOR while the patient is in remission, is still being debated. Randomized controlled trials have reported conflicting results. In TAXIT, adult CD and ulcerative colitis (UC) patients were randomized to continued maintenance IFX therapy either based on TDM-guided dosing or clinically based dosing. The study did not find any difference in the proportion of patients in clinical and biochemical remission after 1 year.[15] In the PAILOT study, pediatric patients with CD were randomized either to proactive monitoring and adalimumab dose intensification to a serum concentration greater than 5 µg/mL or standard dosing for a duration of 72 weeks.[16] The rate of corticosteroid-free clinical remission was significantly higher in the proactive than the standard dosing group (82% vs 48% P = .002). Strik et al demonstrated in PRECISION, that inflammatory bowel disease (IBD) patients (n = 80) randomized to receive a proactive adjustment of IFX level to a target of 3 µg/mL via a pharmacokinetic dashboard had a superior outcome compared to standard dosing. After 1 year, 88% of patients in the proactive group were in sustained clinical remission vs 64% in the standard care group.[17]

In addition, there is emerging evidence that biologic TDM can be used in the proactive setting to determine the appropriateness of treatment de-escalation. A retrospective study in 2015 showed that the withdrawal of immunomodulators (IMM) after at least 6 months of combined treatment with IFX did not reduce the IFX trough levels in patients with CD.[18] Detectable trough levels of IFX at the time of IMM withdrawal were associated with long-term response. Similarly, a prospective study of 96 patients with IBD found that the risk of relapse was reduced if a de-escalation decision was based on clinical, biochemical remission and a trough IFX level above 7 mg/L vs a decision based on clinical and biochemical remission alone (HR = 0.45, P = .024).[19]

Although existing literature has shown TDM-guided therapeutic decisions to be clinically efficacious, the data have been predominantly cross-sectional and do not determine the clinical sequelae of having TDM available to clinicians.[20,21] The aim of this observational study is to evaluate whether biologic TDM alters clinical decision making and identify the clinical scenarios in which proactive and reactive biologic TDM can be utilized.

Methods

This was a retrospective observational study of prospectively collected data at 2 hospitals. All consecutive instances of anti-TNF drug-level measurement between June 2013 and July 2016 in patients with CD were identified, and the clinical, endoscopic, and laboratory data of each relevant patient were reviewed.

For each patient, baseline demographic and anti-TNF treatment data were collected. Demographic data included gender, age, weight, disease duration, smoking status, age at diagnosis, CD phenotype according to Montreal classification, history of previous surgical resection, and use of concomitant IMM. Indication for drug-level testing was classified as either: "Reactive TDM" comprising of secondary LOR during remission or suspected drug reaction or, "Proactive TDM" comprising of clinical response during induction therapy or clinical remission during maintenance therapy or consideration of IMM or anti-TNF drug withdrawal.

Suspected LOR was defined by the recurrence of clinical symptoms and at least 2 of the following objective markers: elevated fecal calprotectin (FCP) >250 µg/g, elevated C-reactive protein (CRP) >5 mg/L, abnormal imaging, or endoscopically active disease. Remission was defined by physician assessment, a lack of clinical symptoms, and normal biomarkers (FCP <250 µg/g or CRP ≤5 mg/L) or endoscopic remission.

Treatment characteristics included the type of anti-TNF drug, indication for anti-TNF drug, drug dose, and frequency. All anti-TNF drug levels measured were trough, ie, from blood samples drawn immediately prior to drug administration. Testing was performed at the Alfred Hospital, Melbourne using a drug-sensitive enzyme-linked immunosorbent assay (MATRIKS BIOTEK, Ankara, Turkey). The measured trough drug level and the presence and level of antidrug antibodies were recorded. In patients who had multiple drug levels tested, each episode was performed at a different point in time and for a different indication. Hence, each episode was subjected to a different TDM-based decision by the treating clinician and a different empiric decision by the panel of gastroenterologists. For the TDM-guided decisions, a therapeutic range during maintenance was defined as 3–7 µg/mL for IFX and 5–8 µg/mL for ADA trough levels.[15,16]

To assess the clinical utility of the drug levels, a comparison was made between TDM-guided decisions and empiric decisions.

1. TDM-guided decisions: in the IBD outpatient clinics by 1 of the 3 IBD specialists (S.C., W.N., J.M.A.) based on all information including anti-TNF drug level.
2. Empiric decisions: hypothetical management decisions were made at a later date by a panel of gastroenterologists at Liverpool Hospital, based on all clinical, laboratory, imaging, and/or endoscopic information available at the time except the anti-TNF drug level and the actual clinical outcome. The panel comprised 1 general gastroenterologist and 2 expert IBD specialists. Each panel member made decisions separately. Final panel decisions were determined based on the agreement between the 2 expert IBD clinicians. Where the decisions by the 2 IBD specialists were different, the final panel decision was based on the agreement between one of the IBD clinicians and the third panel member.

A discrepancy in the TDM-guided and empiric decisions was defined as a TDM result leading to a management change, which would not have otherwise happened in the absence of TDM.

Statistical Analysis

All categories and subcategories were compared using the chi-square test or Fisher exact test, where appropriate. P values <.05 were considered significant. All statistical evaluations were made using SPSS statistical software.

The Human Research Ethics Committee of each institution approved the study.

Results

A total of 187 drug levels in 108 patients with CD were included. Baseline characteristics of patients are included in Table 1. The majority of patients (82, 75.9%) were on concomitant IMMs, and a small portion of patients (44, 23.5%) had previous exposure to anti-TNF therapy. Thiopurines (59/82) were more commonly used as a concomitant IMM than methotrexate (23/82).

One hundred and ten measurements were performed in the proactive setting: 88 during maintenance while the patient was in remission, 10 during induction while the patient was responding, 11 during consideration of IMM withdrawal, and 1 during consideration of anti-TNF therapy withdrawal. In total, 71 measurements were performed in the reactive setting, 66 during secondary LOR, and 5 during drug reactions. All 6 patients with unspecified or incomplete indications for testing were excluded from the final analysis, though they were included in our descriptive data.

Overall, TDM changed management in nearly half (46.9%) of measurement episodes. Adjustment in anti-TNF dosing differed from empiric decisions in 44 (23.5%) instances (Table 2), the greatest contrast was found in 10.2% of patients where knowledge of anti-TNF drug levels lead to an escalation of anti-TNF dose and an empiric decision lead to no change. Adjustment in IMM therapy differed from empiric decisions in 51 instances (27.3%) (Table 3), the greatest contrast was found in 10.2% of patients where knowledge of anti-TNF drug levels lead to an adjustment of IMM dosage and an empiric decision lead to no change. In 6 (3.2%) instances, both anti-TNF and IMM therapy decisions were changed when anti-TNF levels were available.

Knowledge of an anti-TNF drug level was significantly more likely to alter decision making when performed for reactive TDM (63%; 95% CI 52%–74%) than for proactive TDM (36%; 95% CI 28%–46%; $P = .001$) (Figure 1). In the reactive setting, Table 4, decisions were altered by the measurement of anti-TNF drug level in 64% (42/66) of episodes performed for secondary LOR and 60% (3/5) of episodes for suspected drug reaction. In the proactive setting, decisions were altered most frequently (83%, 10/12) in the consideration of drug withdrawal, and were altered in 31% (30/98) of the episodes performed during clinical response or clinical remission.

TDM influenced management in a significantly higher proportion of patients on IFX compared to ADA (56% vs 35%, $P = .004$, Figure 2A). The percentage of patients where knowledge of anti-TNF drug levels led to changes in IMM dose was significantly greater in IFX than ADA users (37% vs 17% $P = .003$, Figure 2B). A greater number of patients on ADA had a therapeutic 6-thioguanine nucleotide (6TGN) level (6TGN > 235 pmol/8 × 10^8 erythrocytes), compared to patients on IFX (83% vs 61% $P = .02$). There was no significant difference between IFX and ADA with regard to the impact of drug-level knowledge on dosing of anti-TNF agents (26% vs 18% $P = .18$, Figure 2C).

The remaining demographic and treatment factors did not influence the likelihood of TDM changing clinician decision making: age, gender, weight, smoking status, age at diagnosis, disease location, disease phenotype (luminal vs fistulising), previous surgical resection, disease duration, treatment with concomitant IMM, the type of IMM used (thiopurine vs methotrexate) and prior history of anti-TNF agent use.

Table 1. Baseline demographic, disease, and treatment characteristics.

	Study population (n = 108)
Females	55 (50.9%)
Age (yr, median; IQR)	37 (27–53)
Disease duration (yr, median; IQR)	9 (6–14)
Smoking status	
Current smoker	16 (14.8%)
Former smoker	20 (18.5%)
Never smoked	69 (63.9%)
Unknown/not documented	3 (2.8%)
Age at diagnosis (yr, median; IQR)	25.0 (19.0–35.0)
Disease location	
Terminal ileal (L1)	17 (15.7%)
Colonic (L2)	33 (30.6%)
Ileocolonic (L3)	53 (49.1%)
Upper gastrointestinal only (L4)	2 (1.9%)
Isolated perianal disease	3 (2.8%)
Disease behavior	
Non-stricturing, non-penetrating (B1)	45 (41.7%)
Stricturing (B2)	28 (25.9%)
Penetrating (B3)	32 (29.6%)
Isolated perianal disease	3 (2.8%)
Perianal disease (total)	54 (50.0%)
Prior surgical resection	44 (40.7%)
Concurrent use of steroids	13 (12.0%)
Use of concomitant immunomodulator	82 (75.9%)
Thiopurine	59 (54.6%)
Methotrexate	23 (21.3%)
Weight (kg, median; IQR)	77.0 (66.2–91.0)
Type of anti-TNF therapy	
IFX	63 (58%)
ADA	45 (42%)
Infliximab samples	107 (57.2%)
Dose at time of TDM (mg/kg, mean; IQR)	5.3 (0–6.4)
Infliximab samples Infusion interval	
8 weekly	88/107 (47.1%)
6 weekly	13/107 (7.0%)
4 weekly	4/107 (2.1%)
Adalimumab samples	80 (42.8%)
Dose at time of TDM (mg, mean)	40
Injection interval	
Fortnightly	60/80 (32.1%)
Weekly	20/80 (10.7%)
Previous anti-TNF treatment	44 (23.5%)

Abbreviations: ADA, adalimumab; IFX, infliximab; IQR, interquartile range; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.

Discussion

Knowledge of anti-TNF drug levels altered management decisions in a significant proportion (46.9%) of patients in this study. Anti-TNF TDM had more impact in reactive

Table 2. Decisions regarding anti-TNF therapy comparing empiric decision (by panel without drug-level results) and TDM-guided decision made by the treating clinician.

		Anti-TNF therapy decision by treating clinician (with anti-TNF TDM)				
		No action (n = 134)	Dose escalate (n = 36)	Dose de-escalate (n = 7)	Stop anti-TNF (n = 5)	Switch to another biologic drug (n = 5)
Empiric anti-TNF therapy decision by panel	No action (n = 160)	126 (67.4%)	19 (10.2%)	6 (3.2%)	5 (2.7%)	4 (2.1%)
	Dose escalate (n = 25)	8 (4.3%)	16 (8.6%)	1 (0.5%)	—	—
	Dose de-escalate (n = 0)					
	Stop anti-TNF (n = 0)					
	Switch to another biologic drug (n = 2)	—	1 (0.5%)	—	—	1 (0.5%)

Abbreviations: TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.
Red indicates where knowledge of the drug level changed the treatment decision. Non-highlighted data indicate where knowledge of drug level did not change treatment decisions.

Table 3. Decisions regarding IMM therapy comparing empiric decision (by panel without drug-level results) and TDM-guided decision made by the treating clinician.

		IMM therapy decision by treating clinician (with anti-TNF drug-level result)					
		No action (n = 139)	Add IMM (n = 9)	Stop IMM (n = 12)	Optimize IMM dose[a] (n = 22)	Decrease IMM dose (n = 2)	Switch IMM (n = 3)
Empiric IMM therapy decision by panel	No action (n = 164)	128 (68.4%)	4 (2.1%)	9 (4.8%)	19 (10.2%)	1 (0.5%)	3 (1.6%)
	Add IMM (n = 9)	4 (2.1%)	5 (2.7%)	—	—	—	—
	Optimize IMM dose	5 (2.7%)	—	—	3 (1.6%)	1 (0.5%)	—
	Stop IMM (n = 0)						
	Decrease IMM dose (n = 5)	2 (1.1%)	—	3 (1.6%)	—	—	—
	Switch IMM (n = 0)						

Abbreviations: IMM, immunomodulators; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.
[a]IMM was optimized by either increasing IMM dose or adding allopurinol in suspected thiopurine "shunters."
Red indicates where knowledge of the anti-TNF drug level changed the treatment decision. Non-highlighted data indicate where knowledge of drug level did not change treatment decisions.

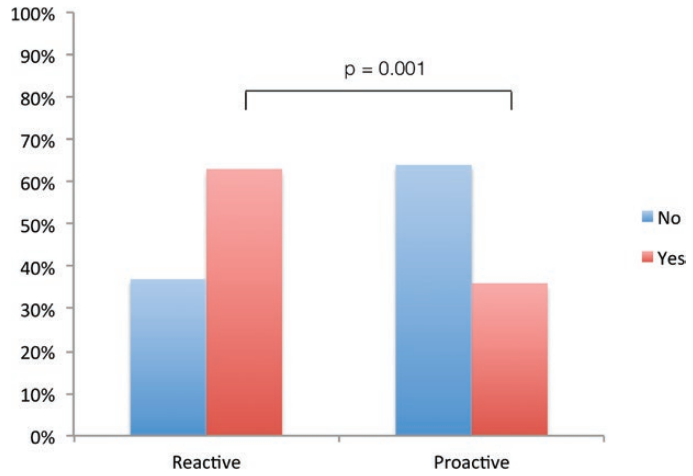

Figure 1. Indications for testing of anti-TNF drug levels and percentage of test episodes where knowledge of drug levels changed management. Abbreviation: TNF, tumor necrosis factor.

TDM, affecting management decisions in 63% of patient episodes, while for proactive indications TDM changed management decisions in 36% of episodes. At the time of our study, many observational studies have supported the use of proactive TDM but the results of 2 RCTs, TAXIT and TAILORIX were inconclusive.[15,22] Subsequent to the completion of our study, the PAILOT study has demonstrated that pediatric CD patients are more likely to obtain steroid-free remission when proactive rather than reactive TDM is utilized.[16]

Our data indicate that TDM altered clinical decision making in a significantly greater portion of patients treated with IFX compared to ADA, which was unexpected (Figure 2). One explanation is that patients on ADA were less likely to require a decision to optimize IMM given a significantly greater proportion of patients already had a therapeutic 6TGN level compared to IFX. This is supported by the fact that measuring anti-TNF drug levels resulted in changes in IMM dose in a significantly higher proportion of patients receiving IFX than ADA, but changes in anti-TNF dose occurred at a similar rate. Current literature, including a systematic review, suggests the rates of LOR and the need for dose intensification between IFX and ADA are broadly similar.[23,24] This is consistent with our study; apart from differences in the rate of IMM change, the anti-TNF drug a patient receives does not influence the likelihood in which biologic TDM alters clinical management. Patients receiving ADA seem to have a more severe phenotype, with penetrating disease affecting 32.5% of ADA patients vs 14% IFX patients and a history of prior surgery occurring in 41% ADA patients vs 31% IFX patients. This may have led to patients on ADA receiving more intensive management, leading to a higher proportion of optimized 6TGN levels. The propensity to commence patients on ADA as opposed to IFX when there is a history of compliance may have also been a contributory factor. The median age, weight, and rate of prior anti-TNF experience were comparable between patients on IFX and ADA.

A major strength of our study is the comparison of proactive and reactive TDM utility in clinical decision making, a relationship not explored before in previous studies. As there is more established literature surrounding the usefulness of reactive TDM, it is not surprising that significantly more decisions were altered in the reactive than the proactive setting. However, our study suggests that proactive TDM still has a role in clinical practice as 36% of management decisions were changed when proactive TDM was performed. In fact, the indication associated with the highest proportion of decisions changed by anti-TNF drug measurements was in the

Table 4. Indications for testing of anti-TNF drug levels and percentage of test episodes where knowledge of drug levels changed management.

	Percentage of decisions altered by knowledge of anti-TNF levels
Reactive	
Secondary loss of response	42/66 (64%)
Suspected drug reaction	3/5 (60%)
Proactive	
Clinical response or remission	30/98 (31%)
Consideration of drug withdrawal	10/12 (83%)

Abbreviation: TNF, tumor necrosis factor.

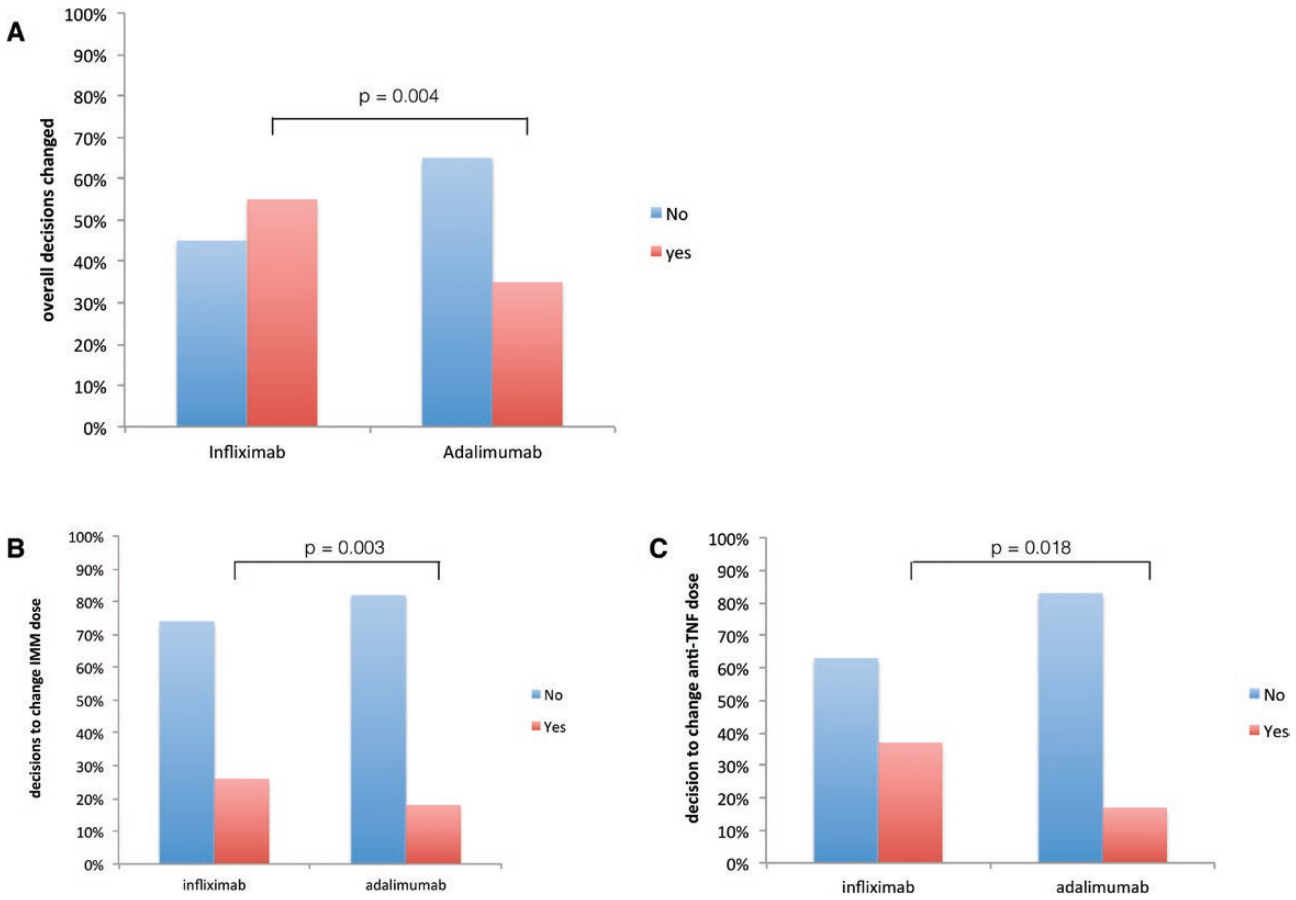

Figure 2. (A) The relationship between drug received and percentage of overall test episodes where knowledge of drug levels changed management (B) The relationship between drug received and percentage of test episodes where knowledge of drug levels led to changes in IMM dose (C) The relationship between drug received and percentage of test episodes where knowledge of drug levels led to changes in anti-TNF dose. Abbreviations: IMM, immunomodulators; TNF, tumor necrosis factor.

proactive scenario of considering drug withdrawal. If future prospective evidence supports the value of proactive TDM, its utility may continue to rise.

The real-life decisions made by the clinicians in our study were based on the knowledge of the anti-TNF drug levels as well as clinical, endoscopic, and laboratory data. Huang et al evaluated how IFX trough levels could affect clinical decision making in IBD patients receiving maintenance IFX therapy. In contrast, real-life management decisions based on clinical data alone without IFX trough level were compared to decisions based solely on a hypothetical IFX trough level algorithm, with a difference of 69.4%.[25] One of the strengths of our study is that it is more reflective of real-world practice where clinicians combine many clinical parameters including anti-TNF drug levels to make a management decision rather than use an algorithm consisting of IFX trough level alone. Selinger et al showed that un-blinding clinicians to a biologic TDM measurement in a virtual clinic lead to a change in one-third of decisions made, however, there was no distinction between proactive and reactive TDM.[26]

Our study is limited by the use of conservative anti-TNF therapeutic ranges, the absence of endoscopic data in some patients, and the measurement of anti-TNF levels with a drug-sensitive assay. The therapeutic ranges defined for IFX and ADA concentrations of 3–7 µg/mL and 5–8 µg/mL, respectively, were chosen to target clinical remission. This study was conducted from 2013 to 2016, and since then there has been a shift towards targeting mucosal healing as a therapeutic endpoint. Mucosal healing is associated with higher therapeutic thresholds of IFX and ADA trough levels.[21,27] It is important to emphasize that the therapeutic range described above served only as guidance to the requesting clinicians using TDM to make real-life decisions. Another limitation is that the ELISA assay, MATRIKS BIOTEK, used in the study was a drug-sensitive assay without the capacity to detect antidrug antibodies in the presence of therapeutic drug levels. This is however a small disadvantage, as most additional antidrug antibodies detected by drug-tolerant assays lack neutralizing capacity and the clinical significance of non-neutralizing antidrug antibodies is unclear.[28]

Conclusion

Measurement of anti-TNF drug levels, in addition to symptomatic, endoscopic, radiologic, and biochemical assessment alters clinical management of adults with CD in both the proactive and reactive setting. Impact on decision making is most prominent when testing is performed for consideration of drug withdrawal, a proactive indication, and secondary LOR, a reactive indication. These findings highlight the importance of incorporating anti-TNF drug-level testing into the standard care of CD patients.

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Author Contributions

All authors have contributed to and agreed on the content of the manuscript. Y.W. performed the statistical analysis and wrote the manuscript. A.W. and S.P.S. performed data collection. W.X. and J.H.K. performed the statistical analysis. S.C., W.N., A.-J.W., and J.M.A. recruited the patients. S.C., W.N., and J.M.A. designed the study and edited the manuscript.

Conflicts of Interest

S.C. has received honoraria for advisory board participation, received speaker fees, educational and/or research support from AbbVie, BMS, Celgene, Celltrion. Ferring, Gilead, Janssen, MSD, Novartis, Pfizer, and Takeda. She has received speaker fees from AbbVie, Janssen, Shire, Ferring, Takeda, and Pfizer and educational support from Orphan, Pfizer, Shire, and Takeda. W.N. is part of the GENIUS group that received funding from Abbvie, Janssen, and Takeda and has received speaker fees from Abbvie and Takeda. J.M.A. is on advisory boards and has received speaker fees from Abbott, Abbvie, Allergan, AstraZeneca, Bayer, Celgene, Ferring, Gilead, Hospira, ImmunsanT, Janssen, MSD, Nestle, Pfizer, Shire, and Takeda. A.-J.W. has received honoraria from Takeda, Janssen, and Abbvie and honoraria and grant support from Ferring. The Liverpool Hospital IBD Service has received research or project funding from AbbVie, Ferring, Janssen, Orphan, Shire, Pfizer, Takeda. Y.W., A.W., S.P.S., W.X., and J.H.K. do not have any conflict of interest to declare.

Data Availability

No new data were created or analyzed.

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